Acetylenic Bond Participation in Biomimetic Polyene Cyclizations.[1,2] Model Studies Directed toward the Synthesis of 20-Keto Steroids. Synthesis of *dl*-Progesterone and *dl*-Δ^4-Androstene-3,17-dione[3]

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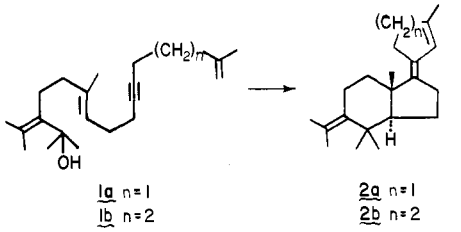
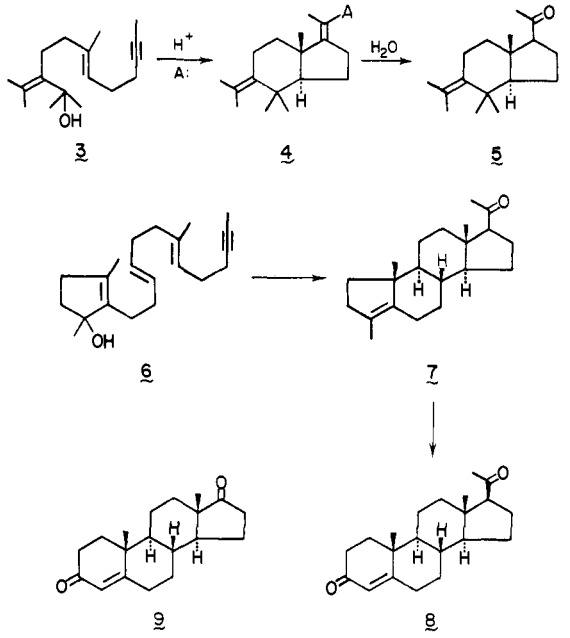
Abstract: The object of this study was to examine the possibility that an appropriately disposed acetylenic bond would participate in biomimetic polyene cyclizations so as to generate the five-membered D ring of steroids. Treatment of the dienynol **3** (synthesized as shown in Scheme I) with anhydrous formic acid in pentane for 15 min at 20 °C resulted in an 82% yield of the bicyclic enol formate **19**. Hydrolysis of **19** gave a mixture of the ketone **21** and its C-1 epimer. When substrate **3** was stirred with 1% trifluoroacetic acid in acetonitrile at −30 °C for 0.5 h, it was completely converted to the enamide **22**, which also gave the ketone **21** upon hydrolysis. Confirmation of the trans-fused hydrindan skeleton of both **19** and **22** was established by oxidative degradation to the known dione **20**. The successful cyclization of the model substrate **3** led to a study of the trienynol **6** which was synthesized by a convergent route, the key step being the stereoselective Wittig–Schlosser condensation of aldehyde **31** (synthesized as shown in Scheme II) with the phosphorane **36** (constructed by the route depicted in Scheme III). The product **37** was converted in three steps to substrate **6** as shown in Scheme IV. When the substrate **6** was treated with trifluoroacetic acid in 10:1 1,2-dichloroethane–ethylene carbonate for 3 h at 0 °C, a 71% yield of the tetracyclic ketone **40** was obtained. Conversion of **40** to *dl*-progesterone (**8**) was effected in 41% yield by ozonolysis (to give **41**) followed by intramolecular aldol condensation. When the cyclization of **6** was conducted in 7.5:1 pentane–1,2-dichloroethane at 0 °C for 1 h, the enol trifluoroacetate **42** was isolated in 78% yield. Ozonolysis (to give **43**) followed by cyclodehydration gave the androstenedione **9**.

It was shown in the preceding study[5] that the acid-catalyzed cyclization of both trienynols **1a** and **1b** involves participation of the acetylenic bond so as to form a five-membered ring thereby generating the trans-fused hydrindan systems **2a** and **2b**, respectively. These results have prompted us to examine the possibility of employing an appropriately positioned and substituted acetylenic bond in a cyclization to give the five-membered D ring of steroids. To this end the cyclization behavior of the model substrate **3**, having a terminal methylacetylenic moiety, was explored first. Unlike the cyclization of **1a** and **1b**, it was expected that termination of the cyclization of **3** would require the presence of an external nucleophile (A). Provided that the nucleophile (A) became bonded to the vinyl group via a heteroatom, it was anticipated that the cyclization product **4** would be susceptible to hydrolysis, giving methyl ketone **5**. In this event a suitable tetracyclic precursor such as **6**[6] might be expected to behave similarly leading to the ketone **7**, which should be readily converted[7] to the important pregnancy hormone progesterone (**8**). These aims have, in fact, been realized, and the present paper constitutes a detailed account of this study which has culminated in an efficient synthesis of the steroids *dl*-progesterone (**8**) and *dl*-Δ^4-androstene-3,17-dione (**9**).



1a n=1
1b n=2

2a n=1
2b n=2

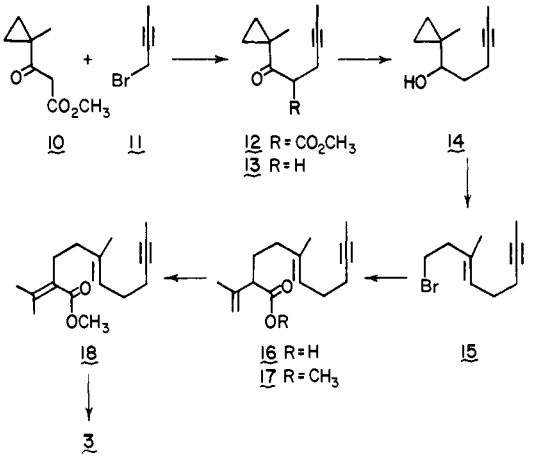


3 4 5

6 7

9 8

Scheme I



10 11 12 R=CO2CH3 13 R=H 14

18 16 R=H 17 R=CH3 15

3

Synthesis and Cyclization of the Model Substrate 3. The synthesis of the allylic alcohol **3** was accomplished by a route (see Scheme I) similar to that employed in the construction of trienynols **1a** and **1b**,[5,8] Thus alkylation of the sodium enolate

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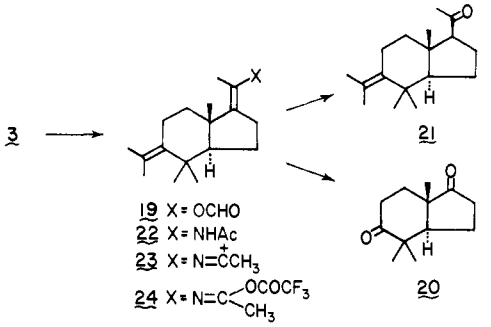
of cyclopropyl keto ester **10** with 1-bromo-2-butyne (**11**)[9] in acetonitrile gave the keto ester **12** which was decarbomethoxylated with barium hydroxide in refluxing ethanol to afford the ketone **13** in 82% overall yield after distillation. Reduction of **13** with lithium aluminum hydride resulted in a 98% yield of the carbinol **14**. Stereoselective rearrangement of alcohol **14** to the trans bromoenyne **15** was accomplished by the modified Julia olefin synthesis.[10] Thus a solution of **14** in 1:1 ether–acetonitrile containing *s*-collidine was treated with zinc bromide and phosphorus tribromide at −70 °C, followed by a further treatment with an additional portion of zinc bromide at 20 °C, to afford the rearranged trans bromide **15** in 96% yield containing less than 1% of the corresponding cis isomer.

The dianion formed by treatment of lithium 3-methyl-2-butenoate with lithium diisopropylamide was alkylated with the bromide **15** to give the crude acid **16,** which was esterified with ethereal diazomethane to afford the β,γ-unsaturated ester **17** in 83% yield after chromatography. Equilibration with potassium *tert*-butoxide in *tert*-butyl alcohol resulted in a 90% yield of a 9:91 mixture of the β,γ- and the α,β-unsaturated esters **17** and **18,** respectively. Three successive treatments with methyllithium afforded a quantitative yield of the desired allylic alcohol **3** contaminated with 7–8% of the corresponding homoallylic alcohol.[11] This mixture was used directly in the cyclization studies described below.

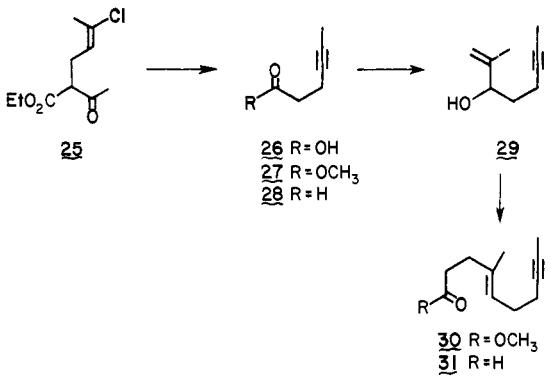
When a solution of the dienynol **3** in dry pentane was stirred with a large excess of formic acid[12] for 15 min at 20 °C, an oily product, consisting of 93% of a single component by VPC, was isolated in 82% yield by preparative TLC. The analytical and spectral data (see Experimental Section) for this material were consistent with the product of a cyclization in which formate had acted as the nucleophile to terminate the process giving the enol formate **19**. Confirmation of this structure was ob-



tained by its degradation to the known *trans*-hydrindandione **20**[5] upon oxidation with excess ruthenium tetroxide in carbon tetrachloride.[13] Hydrolysis of **19** was smoothly effected with dilute aqueous sodium bicarbonate in methanol to give a 9:1 mixture of ketone **21** and its C-1 epimer in 74% yield. The structure assigned to **21** was supported by its analytical and spectral data. The C-1 acetyl moiety was indicated by a carbonyl absorption at 5.85 μ in the IR spectrum and a three-proton singlet at δ 2.10 in the NMR spectrum. The β-acetyl epimer was presumed to be predominant by analogy to the well-known stabilities of the C-17 epimers in the 20-ketopregnane series.

Facile cyclization of dienynol **3** was also effected by treatment with 1% trifluoroacetic acid in acetonitrile for 30 min at −30 °C. VPC examination of the crude product indicated complete conversion of **3** into a new substance which was isolated as an oil in 72% yield by preparative TLC. This substance was formulated as the enamide **22** based on the following spectral and chemical evidence. The NMR spectrum of **22** was similar to that of enol formate **19,** exhibiting sharp three-proton singlets at δ 0.95, 1.17, and 1.27 for the three methyl groups attached to the quaternary carbons C-8 and C-4, singlets for

Scheme II



the methyls of the isopropylidene group at δ 1.70 and 1.80, and a singlet at δ 1.97 for the methyl of the C-1 ethylidene group. In addition, singlets appeared at δ 2.00 for the methyl of the acetamido group and at δ 6.34 for the exchangeable hydrogen bound to nitrogen. The IR spectrum displayed an amide carbonyl absorption at 6.0 μ. Ruthenium tetroxide degradation of the enamide afforded the dione **20,** and hydrolysis of **22** with aqueous hydrochloric acid in methanol resulted in an 11:1 ratio of the 1β-acetylhydrindan **21** and its 1α isomer. This ratio was changed to 9:1 upon equilibration with aqueous sodium hydroxide in methanol.

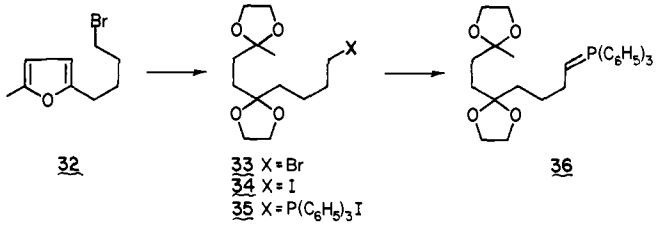
Formation of the enamide **22** may be envisaged as proceeding via a process in which acetonitrile acts as the terminating nucleophile in the cyclization to give the nitrilium ion **23,**[14] reaction of which with trifluoroacetate would yield the imino ester **24.** The latter substance, on treatment with water (in the workup), would be readily hydrolyzed to **22.** Although the geometrical configuration about the double bond attached to the five-membered ring in both **19** and **22** is not known, there is evidence from studies of similar systems[15] to presume trans addition to the carbon–carbon triple bond thereby resulting in the configuration as depicted.

Synthesis of *dl*-Progesterone and *dl*-Δ^4-Androstene-3,17-dione. The successful cyclization of the model substrate **3** set the stage for studying the synthesis of *dl*-progesterone (**8**) via cyclization of the trienynol **6,** which was envisaged as being obtainable by a convergent synthesis (see Scheme IV), the key step being a stereoselective Wittig condensation of the aldehyde **31** with the phosphorane **36** to yield the diketal **37.**

The required aldehyde **31** was synthesized by the route shown in Scheme II. The allylic alcohol **29** was prepared either by reaction of methacrolein with the Grignard reagent from 1-bromo-3-pentyne, or perferably by the method described in detail here. Thus ethyl acetoacetate was alkylated with commercial 1,3-dichloro-2-butene to give the acyl ester **25.**[16] The crude alkylation product underwent deacylation, elimination, and hydrolysis upon treatment with potassium hydroxide, first in refluxing ethanol and then at 130–135 °C in ethylene glycol and 2-ethoxyethanol, to give 4-hexynoic acid (**26**) in 60% overall yield. Acid-catalyzed esterification with methanol in refluxing methylene chloride[17] gave the corresponding methyl ester **27** in 77% yield, which was reduced directly to the aldehyde **28** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al). Interaction of the crude aldehyde with isopropenylmagnesium bromide resulted in an 85% yield (from **27**) of the allylic alcohol **29** contaminated with ca. 15% of 4-hexynol. Conversion of **29** into the required aldehyde **31** was effected in 43% overall yield by the orthoacetate Claisen reaction[18] followed by reduction of the resulting enyne ester **30** with Red-Al.

Construction of the phosphorane **36** was achieved by the route shown in Scheme III. Treatment of 2-methylfuran with *n*-butyllithium in THF followed by alkylation[19] with 1,4-

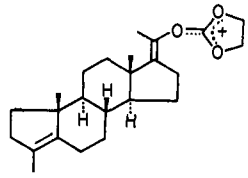
Scheme III



dibromobutane afforded the furan **32** in 73% yield. Concomitant cleavage of the furan ring and ketalization was effected readily by a method developed by W. R. Bartlett involving heating a benzene solution of **32** with ethylene glycol in the presence of *p*-toluenesulfonic acid. The resulting diketal **33** was obtained in 88% yield after chromatography. The corresponding iodide **34,** which was produced in 97% yield by reaction of **33** with sodium iodide in 2-butanone at 80 °C, was treated with triphenylphosphine in benzene for 11 h at 80 °C to afford the crystalline phosphonium salt **35** in 94% yield.

The Wittig condensation of the aldehyde **31** with the phosphorane **36** was performed according to the modification of Schlosser[20] for producing trans olefinic bonds. A suspension of the phosphonium iodide **35** in THF was treated with 1 mol equiv of phenyllithium to give a solution of the ylide **36.** Addition of the acetylenic aldehyde **31** to the ylide solution at −70 °C followed by an additional mol equiv of phenyllithium at −30 °C gave, after final treatment with methanol, the condensation product **37** (see Scheme IV). The crude product was deketalized with dilute aqueous hydrochloric acid in methanol to afford the dione **38,** which was submitted directly to aldol cyclization with 2% aqueous sodium hydroxide in methanol. The product was chromatographed on Florisil to afford the *trans,trans*-cyclopentenone **39** in 46% overall yield from the aldehyde **31.** VPC analysis of this material showed it to contain less than 3% of the corresponding cis,trans isomer, an authentic comparison specimen of which was obtained by performing the normal Wittig condensation of **31** and **36.** The tetracyclic substrate **6** was obtained in 99% yield upon treatment of an ethereal solution of the ketone **39** with methyllithium. Since this tertiary allylic alcohol was highly susceptible to dehydration, it was used directly in the cyclization step without purification.

Cyclization of the trienynol **6** was conducted in 10:1 1,2-dichloroethane–ethylene carbonate. It was hypothesized that ethylene carbonate might serve as a nucleophilic agent to terminate the cyclization process, forming a stabilized cation A which would collapse to give a methyl ketone upon aqueous

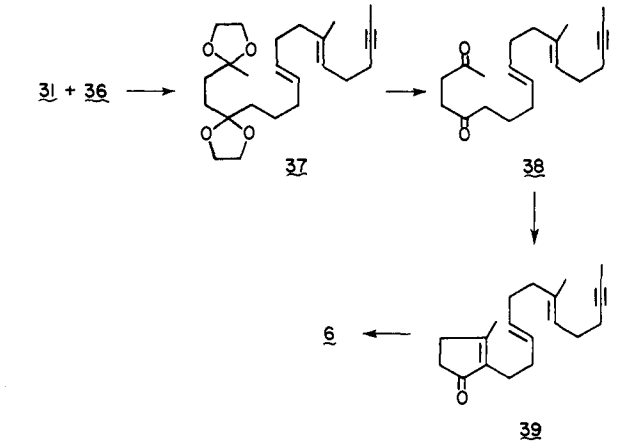


A

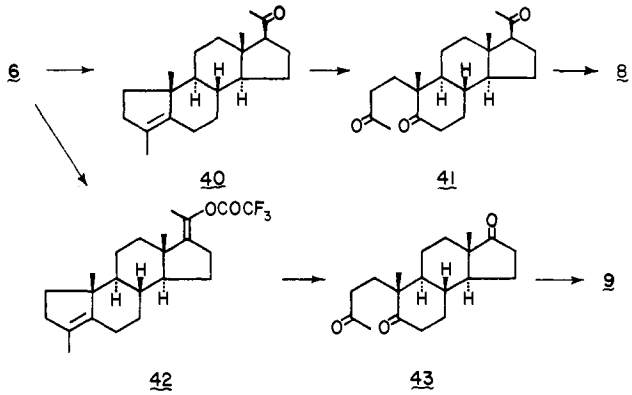
workup. The substrate solution was stirred with a large excess of trifluoroacetic acid for 3 h at 0 °C and the resulting deep-red mixture was neutralized with potassium carbonate in aqueous methanol. VPC examination of the crude product showed it to be a mixture consisting of 70% of the 17β ketone **40,** 13% of the 17α isomer, 6% of the tetraenyne resulting from elimination of water from **6,** and 11% of unidentified components.[21] A 5:1 mixture of the 17β/17α ketones was isolated in 71% overall yield from enone **39** by column chromatography.

The constitution of the tetracyclic ketone **40** was established by its conversion to progesterone (**8**), which was patterned after the route employed in another series.[7] Thus the C-17 epimeric

Scheme IV



Scheme V



mixture of ketones was ozonized at −70 °C in methylene chloride–methanol to give the crude triketone **41** in 88% yield. This material was submitted to intramolecular aldol cyclodehydration with 5% aqueous potassium hydroxide in methanol. Purification of the product by preparative TLC afforded a crystalline solid in 45% yield (from **40**) consisting of 85% *dl*-progesterone (**8**) and 15% of the 17α isomer. Two recrystallizations afforded colorless prisms, mp 182–185 °C, undepressed on admixture with an authentic specimen of *dl*-progesterone.[22] The IR, NMR, and mass spectra of the synthetic material were identical with the corresponding spectra of naturally derived progesterone.

When the trienynol **6** was treated with a large excess of trifluoroacetic acid in 7.5:1 pentane–1,2-dichloroethane for 1 hr at 0 °C, the product, isolated in 78% yield by preparative TLC, appeared to be the enol trifluoroacetate **42,** as suggested by the NMR and IR spectra (see Experimental Section), as well as by the following conversion. Ozonolysis of this product gave a mixture of triketones **43,** which was submitted to aldol cyclodehydration to afford an oil consisting of 78% androstenedione **9,** 7% of *dl*-progesterone (**8**), and 15% of an unidentified substance.[21] The crude product was purified by preparative TLC to give a 52% yield of dione **9,** which, after two recrystallizations, afforded colorless crystals, mp 128–130 °C, undepressed on admixture with authentic *dl*-Δ^4-androstene-3,17-dione.[23] The IR spectra of the two specimens were identical.

The successful syntheses of *dl*-progesterone and *dl*-Δ^4-androstene-3,17-dione via biomimetic cyclization of the trienynol **6** demonstrate the efficacy of acetylenic bond participation in generating the five-membered D ring of the steroid nucleus. Other steroid syntheses via polyene cyclization involving acetylenic participation have been announced in preliminary disclosures, and full accounts of these studies are forthcoming.

Experimental Section[24]

General Considerations. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. NMR spectra were recorded under the supervision of Dr. L. J. Durham on Varian Associates T-60 and XL-100 spectrometers. Deuteriochloroform was used as the solvent and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane = 0. Mass spectra were determined on an Atlas CH-4 spectrometer under the supervision of Dr. A. M. Duffield. Infrared (IR) spectra were recorded on Perkin-Elmer Models 137 and 421 spectrometers and ultraviolet (UV) spectra were recorded on a Cary Model 14 spectrometer using 1-cm quartz cells. Vapor phase chromatographic (VPC) analyses were performed on a Hewlett-Packard HP 402 chromatograph using the following $\frac{1}{8}$ in. glass columns: 4-ft 5% SE-30 and 3.5-ft 3.8% SE-30 on Chromosorb W.H.P. and 6 ft 3% XE-60 on Gas-Chrom Q. Helium was used as the carrier gas and disk chart integrations are uncorrected for detector response. Analytical and preparative thin layer chromatography (TLC) was performed using silica gel GF_{254} or HF_{254} (E. Merck AG) as the absorbent at 0.25- and 1.0-mm thicknesses, respectively. Analytical plates were visualized by spraying with a solution of 2% ceric sulfate in 2 N sulfuric acid, then heating the plate at 180 °C for 5–10 min. "Evaporative distillation" refers to bulb-to-bulb short-path distillation in which the bulb was heated in a hot-air oven (Buchi Kugelrohrofen). The cited temperatures for these distillations refer to the maximum temperature attained by the oven during the distillation and are thus not true boiling points.

1-(Methylcyclopropyl) 1-Carbomethoxy-3-pentynyl Ketone (12). A solution of 13.6 g (0.10 mol) of 1-bromo-2-butyne (**11**),[9] n^{25}_D 1.504,[25] in 20 mL of acetonitrile (distilled from calcium hydride) was added via syringe to a slurry of 15.0 g (0.10 mol) of sodium iodide in 10 mL of acetonitrile. The mixture was stirred for 30 min at room temperature; then a solution of the sodium enolate of 1-methylcyclopropyl carbomethoxymethylene ketone (**10**), prepared from 17.7 g (0.12 mol) of the ketone and sodium hydride, in 70 mL of acetonitrile was added over a period of 30 min. The resulting mixture was stirred for 3 h at room temperature and was then heated at 50–60 °C overnight. The mixture was cooled, poured into dilute hydrochloric acid, and extracted with ether[24] to give 29.6 g of yellow oil consisting of 60–65% of the desired keto ester **12**, 10% of the starting ketone **10**, and 25% of unidentified material as shown by VPC (4-ft 5% SE-30, 100 °C).

An analytical sample was obtained by preparative TLC; IR λ_{max} (film) 3.42, 5.71 (ester C=O), and 5.90 μ (C=O); NMR 0.84 (m, 2 H, cyclopropyl H's), 1.39 (m, 2 H, cyclopropyl H's), 1.40 (s, 3 H, cyclopropyl CH_3), 1.73 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.63 (m, 2 H, $\equiv CCH_2-$), 3.71 (s, 3 H, CO_2CH_3), and 3.78 ppm (t, J = 7 Hz, 1 H, $CHCO_2CH_3$); TLC R_f 0.21 (9:1 hexane–ethyl acetate).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; Found: C, 69.10; H, 7.79.

1-(Methylcyclopropyl) 3-Pentynyl Ketone (13). A solution of 28.0 g (containing 60–65% ester) of the crude keto ester **12** in 200 mL of 95% ethanol was added to a solution of 64.0 g (0.40 mol) of barium hydroxide octahydrate in 600 mL of water. The resulting mixture was heated at reflux for 20 h under nitrogen, cooled, and poured into 1000 mL of 10% aqueous hydrochloric acid. Dilution with 600 mL of brine and extraction with benzene using a base wash[24] gave 17.7 g of yellow oil, which was comprised of 75–80% of the desired ketone **13** as shown by VPC (4-ft 5% SE-30, 100 °C). Distillation through a Vigreux column afforded 11.7 g (82% yield from 1-bromo-2-butyne) of ketone **13** as a colorless oil, bp 60–63 °C (0.05 mm), which was >95% pure by VPC.

An analytical sample was obtained by evaporative distillation of the distilled material at 75 °C (0.05 mm): n^{21}_D 1.4744; IR λ_{max} ($CHCl_3$) 3.42, 5.92 (C=O), and 9.22 μ; NMR 0.74 (m, 2 H, cyclopropyl H's), 1.24 (m, 2 H, cyclopropyl H's), 1.36 (s, 3 H, cyclopropyl CH_3), 1.72 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), and 2.50 ppm (m, 4 H, CH_2CH_2 CO).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.92; H, 9.41.

1-(Methylcyclopropyl)-3-pentynylcarbinol (14). A solution of 5.60 g (37.3 mmol) of the distilled ketone **13** in 100 mL of dry ether was added to a cold (0 °C) suspension of 2.0 g (52.7 mmol) of lithium aluminum hydride in 200 mL of dry ether. The mixture was stirred at 0 °C for 1 h, then ethyl acetate was added cautiously to decompose the excess hydride. The mixture was poured into water and extracted with ether[24] to afford 5.56 g (98% yield) of the carbinol **14** as a colorless oil which was 95% pure by VPC (4-ft 5% SE-30, 100 °C).

A small sample was evaporatively distilled at 75 °C (0.05 mm) to afford an analytical specimen: n^{21}_D 1.4600; IR λ_{max} ($CHCl_3$) 2.70–3.23 (OH), 3.39, and 9.39 μ; NMR 0.37 (m, 4 H, cyclopropyl H's), 1.02 (s, 3 H, cyclopropyl CH_3), 1.30 (br s, 1 H, OH), 1.68 (m, 2H, $CH_2CH(OH)$), 1.72 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.30 (m, 2 H, $\equiv CCH_2-$), and 2.98 ppm (t, J = 6 Hz, 1 H, $CH(OH)$); TLC R_f 0.31 (9:1 hexane–ethyl acetate).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.93; H, 10.63.

1-Bromo-3-methyl-*trans*-3-nonen-7-yne (15). A modification of a published procedure[10] was employed. A solution of 1.52 g (10 mmol) of the carbinol **14** (95% pure by VPC) in 200 mL of 1:1 ether–acetonitrile was added to 10.1 g (50 mmol) of flame-dried zinc bromide followed by 2.50 mL (20 mmol) of *s*-collidine. The mixture was mechanically stirred under nitrogen and cooled to −70 °C; then 1.0 mL (10 mmol) of phosphorus tribromide in 5 mL of ether was added dropwise over a period of 5 min. The dry ice bath was replaced with an ice bath and the mixture was stirred for 4 h at 0 °C. An additional 10.1 g (50 mmol) of zinc bromide was introduced, and stirring was continued at room temperature for 2 h, then 1.2 mL (15 mmol) of pyridine followed by 200 mL of water was added. Extraction with ether using an acid wash[24] gave 2.05 g (96% yield) of pale yellow oil consisting of 94% of the trans bromide **15**, 0.6% of the presumed cis isomer, and unrearranged bromides as shown by VPC (4-ft 5% SE-30, 100 °C).

Chromatography on Florisil (pentane) followed by evaporative distillation at 70 °C (0.025 mm) afforded an analytical sample: n^{21}_D 1.4921; IR λ_{max} (film) 3.42, 6.94, 7.87, and 8.26 μ; NMR 1.64 (s, 3 H, vinyl CH_3), 1.76 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.18 (m, 4 H, H's at C-5 and C-6), 2.54 (t, J = 7 Hz, 2 H, C-2 CH_2), 3.41 (t, J = 7 Hz, 2 H, C-1 CH_2), and 5.27 ppm (t, J = 6 Hz, 1 H, vinyl proton); TLC R_f 0.66 (9:1 pentane–ethyl acetate).

Anal. Calcd for $C_{10}H_{15}Br$: C, 55.83; H, 7.03. Found: C, 55.84; H, 6.82.

Methyl 2-Isopropylidene-5-methyl-*trans*-undec-5-en-9-ynoate (18). A solution of 4.04 g (40 mmol) of diisopropylamine in 10 mL of dry THF was cooled to 0 °C and 16 mL (40 mmol) of a 2.50 M solution of *n*-butyllithium in hexane was added. The resulting solution was stirred at 0 °C for 5 min; then it was added via syringe to a cold (0 °C) mixture of 4.24 g (40 mmol) of lithium 3-methyl-2-butenoate[8] in 30 mL of dry THF. The resulting mixture was stirred for 15 min at 0–10 °C and cooled to −70 °C, and a solution of 2.30 g (10 mmol) of the crude bromide **15** in 20 mL of dry THF was introduced via syringe over a period of 3 min. The mixture was stirred at −70 °C for 10 min, then at 0 °C for 4 h, and overnight at room temperature. The reaction mixture was poured into 200 mL of 5% aqueous sodium hydroxide and washed with 1:1 ether–pentane (3 × 100 mL). The combined organic layers were extracted with 40 mL of water, and the combined aqueous layers were cooled to 0 °C and acidified to pH 1.0 with 10% hydrochloric acid. Extraction with benzene[24] afforded 3.10 g of crude acid **16** as a yellow oil.

This crude acid was methylated with excess ethereal diazomethane to give 3.20 g of yellow oil consisting of 74% of the β,γ-unsaturated ester **17**, 3.5% of presumably γ-alkylation product, 5.5% of methyl 3-methyl-2-butenoate, and 11 % of isophorone as estimated by VPC (4-ft 5% SE-30, 160 °C). Chromatography on Florisil (pentane) afforded 2.05 g (83% yield from bromide **15**) of β,γ-unsaturated ester **17** (95% pure by VPC) as a pale yellow oil. This material was not further characterized, but was equilibrated directly as described below.

The chromatographed ester was dissolved in 25 mL of dry *tert*-butyl alcohol, and 10 mL of a 5% solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added via syringe. The mixture was stirred under nitrogen for 6 h at room temperature, then poured into a mixture of dilute hydrochloric acid and brine. Extraction with pentane[24] followed by evaporative distillation at 100–150 °C (0.01 mm) afforded 1.84 g (90% yield) of colorless oil which was a 9:91 mixture of β,γ- and α,β-unsaturated esters **17** and **18** as shown by VPC (4-ft 5% SE-30, 160 °C).

An analytical sample of **18** was obtained after evaporative distillation at 100–150 °C (0.01 mm) and preparative TLC: IR λ_{max} (film) 3.41, 5.80 (C=O), 6.01 (C=C), and 8.40 μ; NMR 1.65 (s, 3 H, C-6

vinyl CH_3), 1.78 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 1.85 (s, 3 H, isopropylidene CH_3), 1.97 (s, 3 H, isopropylidene CH_3), 2.18 (m, 8 H, C-4, C-5, C-8, and C-9 CH_2's), 3.74 (s, 3 H, CO_2CH_3), and 5.22 ppm (t, J = 6 Hz, 1 H, C-7 vinyl proton); TLC R_f 0.37 (9:1 hexane–ethyl acetate).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.61; H, 9.73.

3-Isopropylidene-2,6-dimethyldodeca-*trans*-6-en-10-yn-2-ol (3). A few crystals of 1,10-phenanthroline were added to a solution of 109 mg (0.44 mmol) of the distilled α,β-unsaturated ester **18** in 7 mL of ether, and excess methyllithium (2.0 M solution in ether) was added. The deep brown solution was stirred under nitrogen for 5 min; then methanol was carefully added until a lime green color persisted. The mixture was stirred for 5 min and the treatment with methyllithium as above was repeated two more times. The resulting mixture was poured into water and extracted with ether[24] to afford 110 mg (100% yield) of pale yellow oil comprised of 92% of the desired alcohol **3** and 7–8% of the corresponding homoallylic alcohol[11] as shown by VPC (4-ft 5% SE-30, 160 °C): IR λ_{max} (film) 2.74–3.23 (OH), 3.42, and 8.89 μ; NMR 1.48 (s, 6 H, CH_3's attached to C-2), 1.68 (s, 3 H, C-6 vinyl CH_3), 1.76 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 1.84 (s, 3 H, isopropylidene CH_3), 1.99 (s, 3 H, isopropylidene CH_3), 2.19 (m, 8 H, C-4, C-5, C-8, and C-9 CH_2's), and 5.20 ppm (t, J = 6 Hz, 1 H, C-7 vinyl proton). This material was used directly in the cyclization studies described below.

Cyclization of Dienynol 3 with Formic Acid. 1-(α-Formyloxyethylidene)-5-isopropylidene-4,4,8β-trimethyl-9α-hydrindan (19). A solution of 50 mg (ca. 0.11 mmol) of the alcohol **3** (contaminated with 47% of the isomeric homoallylic alcohol[11]), obtained in a manner similar to that described above, in 90 mL of dry *n*-pentane was stirred vigorously while 1.3 mL (35 mmol) of anhydrous formic acid was added. The mixture was stirred under nitrogen for 15 min; then excess aqueous sodium bicarbonate was added. Extraction with *n*-hexane[24] followed by preparative TLC (0.75 mm thick silica gel HF_{254}; R_f 0.53, 9:1 hexane–ethyl acetate) afforded 25 mg (82% yield based on substrate that is 53% pure) of enol formate **19** as a colorless oil which was 93% pure by VPC (3.5-ft 3.8% SE-30, 160 °C).

Evaporative distillation at 95 °C (0.10 mm) gave an analytical sample: IR λ_{max} (film) 5.80 μ (C=O); NMR 0.97 (s, 3 H, C-8 CH_3), 1.12 (s, 3 H, C-4 CH_3), 1.25 (s, 3 H, C-4 CH_3), 1.70 (s, 3 H, isopropylidene CH_3), 1.78 (s, 3 H, isopropylidene CH_3), 1.87 (s, 3 H, ethylidene CH_3), and 8.00 ppm (s, 1 H, OCHO); mass spectrum *m/e* 276 (M^+), 230 ($M - HCO_2H$), and 215 ($M - CH_3 - HCO_2H$).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.48; H, 10.16.

Oxidative Degradation of Enol Formate 19. An adaptation of a published procedure[13] was employed, whereby a solution of 56 mg of the enol formate **19** (purified by preparative TLC, 78% pure by VPC), obtained from another cyclization experiment similar to that described above, in 5 mL of carbon tetrachloride was treated with 10 mL of a solution prepared from 0.8 g of ruthenium dioxide ("57.5%") suspended in 60 mL of carbon tetrachloride. This mixture was stirred for 0.5 h at room temperature; then the excess ruthenium tetroxide was destroyed by the addition of isopropyl alcohol. After stirring for 5 min, the resulting black solid was removed by suction filtration through Celite. The filtrate was evaporated at reduced pressure to afford 15 mg of oil, VPC (3.8% SE-30, 160 °C) examination of which showed the absence of starting material and suggested the presence of hydrindandione **20**. The crude product was dissolved in hot hexane, filtered, seeded with a trace of authentic **20**,[5] mp 57–59 °C, and chilled at −15 °C overnight. Two further recrystallizations from hexane gave 9 mg (29% yield) of dione **20** as colorless crystals, mp 57–59 °C, identical with authentic **20** by IR, TLC and VPC. A mixture of the two specimens melted at 57–59 °C.

Hydrolysis of Enol Formate 19. 1-Acetyl-5-isopropylidene-4,4,8β-trimethyl-9α-hydrindan (21). A mixture of 66 mg (0.23 mmol) of the enol formate **19** (97% pure by VPC), obtained from two cyclization experiments, 8 mL of 5% aqueous sodium bicarbonate solution, and 8 mL of methanol was stirred at room temperature for 12 h. The methanol was removed at the rotary evaporator, and the residue was diluted with water. Ether extraction[24] gave 46 mg (80% yield) of a colorless oil consisting of 92% of a mixture of the two epimeric C-1 methyl ketones **21** by VPC (3.8% SE-30, 160 °C). Preparative TLC (R_f 0.29, 9:1 hexane–ethyl acetate) afforded 30 mg (51% yield) of a 9:1 mixture of methyl ketones **21** which was 95% pure by VPC.

An analytical sample was obtained by evaporative distillation at 65–68 °C (0.05 mm): IR λ_{max} (film) 5.85 μ (C=O); NMR 0.72 (s, 3 H, C-8 CH_3), 1.17 (s, 6 H, C-4 CH_3's), 1.68 (s, 3 H, isopropylidene CH_3), 1.83 (s, 3 H, isopropylidene CH_3), and 2.10 ppm (s, 3 H, acetyl CH_3); mass spectrum *m/e* 248 (M^+), 205 ($M - 43$), and 43 (base peak).

Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.02; H, 11.15.

Cyclization of Dienynol 3 with Trifluoroacetic Acid in Acetonitrile. 1-(α-Acetamidoethylidene)-5-isopropylidene-4,4,8β-trimethyl-9α-hydrindan (22). A solution of 150 mg (ca. 0.42 mmol) of the alcohol **3** (contaminated with 29% of the isomeric homoallylic alcohol[11]) in 75 mL of dry acetonitrile was stirred vigorously at −30 °C under nitrogen while 0.75 mL of trifluoroacetic acid was added. The resulting mixture was stirred at −30 °C for 30 min; then excess aqueous sodium bicarbonate was added. Extraction with ether[24] afforded 135 mg of yellow oil, VPC (3.8% SE-30, 200 °C) examination of which indicated essentially complete conversion of the alcohol **3** into the enamide **22.** The crude product was purified by preparative TLC (R_f 0.45, ethyl acetate) to give 89 mg (72% yield) of **22** which was 95% pure by VPC: IR λ_{max} (film) 6.0 μ (C=O); NMR 0.95 (s, 3 H, C-8 CH_3), 1.17 (s, 3 H, C-4 CH_3), 1.27 (s, 3 H, C-4 CH_3), 1.70 (s, 3 H, isopropylidene CH_3), 1.80 (s, 3 H, isopropylidene CH_3), 1.97 (s, 3 H, ethylidene CH_3), 2.00 (s, 3 H, acetamido CH_3), and 6.34 ppm (s, 1 H, NHCO); UV λ_{max} (EtOH) 212 nm (ϵ 13 900) and 229 (5400); mass spectrum *m/e* 289 (M^+), 274 ($M - 15$), 246 ($M - 43$), 236 ($M - 49$), and 215 ($M - 74$).

Attempts to obtain a satisfactory combustion analysis after purification by evaporative distillation or by repeated preparative TLC were unrewarded. The purified enamide is a colorless liquid, but it rapidly acquires a yellow color and is probably oxygen sensitive.

Oxidative Degradation of Enamide 22. The procedure employed was similar to that described above for the oxidative degradation of enol formate **19.** Thus 16 mg (0.055 mmol) of enamide **22** (95% pure by VPC) was treated with excess ruthenium tetroxide for 4 h to afford 3 mg (26%) of hydrindandione **20** as a colorless oil. This material and an authentic specimen of dione **20** displayed identical IR spectra and exhibited identical VPC and TLC behavior.

Hydrolysis of Enamide 22. A mixture of 61 mg (0.21 mmol) of enamide **22** (95% pure by VPC), 3 mL of methanol, and 3 mL of 2 N aqueous hydrochloric acid was stirred for 8 h at room temperature; then the methanol was removed at reduced pressure and the residue was neutralized with aqueous sodium bicarbonate solution. Extraction with ether[24] afforded 28 mg (42% yield) of an oil consisting of 77% of the epimeric C-1 methyl ketones **21** in ratio of 11:1 as shown by VPC (3.8% SE-30, 160 °C). Preparative TLC (9:1 hexane–ethyl acetate) yielded 13 mg of a mixture of the epimeric methyl ketones **21** that was 95% pure by VPC.

This chromatographed material was equilibrated by dissolution in 2:1 methanol—0.05 N aqueous sodium hydroxide. The methanol was removed at reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. Ether extraction[24] yielded 10 mg of a 9:1 mixture of epimeric methyl ketones **21**, the properties (NMR, VPC, TLC) of which were identical with those of the methyl ketones **21** obtained via hydrolysis of the enol formate **19.**

4-Hexynal (28). An adaptation of a published procedure[16] was employed. A solution of 46.0 g (2 g-atoms) of sodium in 500 mL of absolute ethanol was heated at reflux while 325 g (2.5 mol) of ethyl acetoacetate (practical grade) was added over a period of 30 min. The resulting solution was heated at reflux for 15 min; then 250 g (2.0 mol) of 1,3-dichloro-2-butene, n^{20}_D 1.4675, was added at a rate sufficient to maintain reflux with gentle heating toward the end of the addition. The mixture was stirred while heating at reflux for 4 h; then the ethanol was removed by distillation at atmospheric pressure. The pot residue was allowed to cool to room temperature; then water and 1.2 N hydrochloric acid were added. Extraction with ether[24] gave 485 g of dark yellow oil consisting of 73% of the alkylated product **25,** 20% of ethyl acetoacetate and other volatile components, and 7% of dialkylated product as shown by VPC (3% XE-60, 100 °C). This material was used directly in the deacylation step described below.

A small sample of the above material was purified by preparative TLC (R_f 0.27, 3:1 pentane–ethyl acetate) followed by evaporative distillation at 100 °C (0.1 mm) to afford keto ester **25** as a colorless oil: n^{20}_D 1.4640[26]; IR λ_{max} (film) 2.90, 5.74 (ester C=O), 5.80 ($COCH_3$), and 6.00 μ (C=C); NMR 1.27 (t, J = 7 Hz, 3 H, ester CH_3), 2.12 (m, $W_{h/2}$ = 3 Hz, 3 H, vinyl CH_3), 2.23 (s, 3 H, $COCH_3$),

2.68 (t, J = 7 Hz, 2 H, allylic CH_2), 3.57 (t, J = 7 Hz, 1 H, homoallylic CH), 4.22 (q, J = 7 Hz, 2 H, ester CH_2), and 5.48 ppm (t, J = 7 Hz, 1 H, vinyl proton).

A solution of 264 g (4 mol) of 85% potassium hydroxide in 250 mL of 95% ethanol was heated at reflux while 242 g (1.25 mol) of the crude keto ester **25** was added at a rate sufficient to maintain gentle reflux. The condenser was converted for distillation; then 150 mL of ethylene glycol and 50 mL of 2-ethoxyethanol were added, and ethanol–water was distilled off until the pot temperature reached 130–135 °C. The mixture was stirred at 130–135 °C[27] for 5 h; then it was cooled to 80 °C and 1 L of brine was added. The resulting mixture was stirred at room temperature for 2–3 h, then washed with three portions of ether. The aqueous layer was acidified to pH 6.5 with cold concentrated hydrochloric acid, washed with chloroform, and further acidified to pH 1.0. Extraction with chloroform[24] followed by azeotropic removal of acetic acid with dioxane afforded 67.1 g (60% yield based on 1,3-dichloro-2-butene) of pale brown, crystalline solid consisting of 86% of 4-hexynoic acid (**26**), 10% of sorbic acid, and 4% of 5-chloro-*cis*-4-hexenoic acid as suggested by NMR.

A sample of the crude acid was purified by crystallization from benzene–pentane followed by vacuum sublimation to yield 4-hexynoic acid (**26**) as colorless needles: mp 99–100 °C (reported[28] 100–101 °C); NMR 1.77 (t, J = 3 Hz, 3 H, $\equiv CCH_3$), 2.53 (m, $W_{h/2}$ = 4 Hz, 4 H, C-2 and C-3 CH_2's), and 7.51 ppm (s, $W_{h/2}$ = 7 Hz, 1 H, CO_2H).

A mixture of the above crude acid, 48 g of methanol, 0.50 g of *p*-toluenesulfonic acid monohydrate, and 150 mL of dry methylene chloride was heated at reflux for 20 h. The resulting mixture was cooled, diluted with saturated aqueous sodium bicarbonate, and extracted with ether using a base wash[24] to afford 58 g of orange oil. This material was distilled through a Vigreux column to give 51.0 g of methyl 4-hexynoate (**27**) as a colorless oil, bp 77–78 °C (21 mm) (reported[28] 61.5 °C (10 mm)) which was 95% pure by VPC (5% SE-30, 80 °C): NMR 1.72 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.46 (m, $W_{h/2}$ = 3.5 Hz, 4 H, C-2 and C-3 CH_2's), and 3.67 ppm (s, 3 H, CO_2CH_3).

A solution of 25.0 g (0.20 mol) of the distilled ester **27** in 100 mL of dry THF was placed in a 500-mL flask equipped with a mechanical stirrer and a dry ice–acetone-cooled addition funnel. The solution was stirred at −70 °C under nitrogen while 70 mL (0.50 mol) of a 3.54 M solution of Red-Al (Aldrich Chemical Co.) in benzene, diluted to 140 mL with dry THF, was added over a period of 1 h via the cooled addition funnel. The resulting mixture was stirred for 5 h at −70 °C; then 14.2 mL (11 g, 0.25 mol) of acetaldehyde, bp 20–22 °C, was slowly added via syringe. After stirring for 10 min at −70 °C, the mixture was poured into 100 mL of concentrated hydrochloric acid in 500 mL of saturated brine. Extraction with ether using a base wash[24] followed by drying over 4A molecular sieves afforded the crude aldehyde **28** as a colorless oil which contained 15% 4-hexynol and traces of THF and ethanol by VPC (5% SE-30, 120 °C). This material was used directly in the Grignard reaction described below.

A sample of the crude aldehyde from a similar run was purified by distillation through a Vigreux column to give 4-hexynal (**28**) as a colorless liquid: bp 70 °C (20 mm); n^{20}_D 1.4524; IR λ_{max} (film) 3.42, 3.68 (CHO), 5.77 (C=O), and 9.45 μ; NMR 1.71 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.48 (m, $W_{h/2}$ = 5 Hz, 4 H, C-2 and C-3 CH_2's), and 9.75 ppm (s, $W_{h/2}$ = 3.0 Hz, 1 H, CHO). A satisfactory combustion analysis of this aldehyde could not be obtained, possibly owing to its susceptibility to air oxidation.

The **2,4-dinitrophenylhydrazone** was obtained as yellow needles, mp 119.5–120.0 °C, after two recrystallizations from ethanol–ether.

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.15; H, 4.38; N, 20.28. Found: C, 52.07; H, 4.42; N, 20.51.

2-Methyl-1-octen-6-yn-3-ol (29). A mixture of 14.4 g (0.6 g-atom) of dry magnesium turnings, 1.0 mL of 1,2-dibromoethane, and 70 mL of dry THF was stirred under nitrogen until reaction was initiated; then 36.0 g (0.30 mol) of 2-bromopropene (n^{20}_D 1.4425) was added at such a rate as to maintain reflux without external heating. The resulting mixture was stirred until it had cooled to room temperature; then it was cooled to −15 °C and the crude 4-hexynal (**28**) described above (ca. 0.20 mol) was added over a period of 15 min. The mixture was stirred for 2 h at room temperature; then saturated aqueous ammonium chloride solution was added followed by water. Extraction with ether[24] gave 23.5 g (85% yield based on ester **27**) of pale yellow oil consisting of 85% of the desired allylic alcohol **29**, 13% of 4-hexynol, and 2% of high molecular weight materials as shown by VPC (3% XE-60, 75 °C).

Preparative TLC (R_f 0.70, 2:1 pentane–ethyl acetate) followed by evaporative distillation at 60 °C (0.05 mm) afforded an analytical sample of alcohol **29** as a colorless oil: IR λ_{max} (film) 2.70–3.14 (OH), 3.41, 6.07, and 11.05 μ (C=C); NMR 1.76 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 1.80 (s, 3 H, vinyl CH_3), 1.82 (m, 3 H, C-4 CH_2 and OH), 2.24 (m, 2 H, C-5 CH_2), 4.20 (t, J = 6 Hz, 1 H, C-3 CH), 4.88 (br s, $W_{h/2}$ = 4.0 Hz, 1 H, C-1 vinyl proton), and 5.00 ppm (br s, $W_{h/2}$ = 4.0 Hz, 1 H, C-1 vinyl proton).

Anal. Calcd for $C_9H_{14}O$: C, 78.21 H, 10.21. Found: C, 78.14; H, 10.15.

Methyl 4-Methyl-*trans*-4-decen-8-ynoate (30). An adaptation of a published procedure[18] was employed. A mixture of 11.75 g (72.5 mmol) of the crude allylic alcohol **29**, 53.0 g (440 mmol) of distilled trimethyl orthoacetate, bp 107–108 °C, and 0.50 g (6.7 mmol) of propionic acid was heated at 115 °C under nitrogen for 16 h in a flask equipped with a condenser and a Dean-Stark trap. The mixture was cooled, poured into water, and extracted with ether using a wash with 1.2 N hydrochloric acid[24] to give 14.24 g of orange oil consisting of 79% of the desired ester **30**, 14% of 4-hexynol, and 7% of minor impurities as shown by VPC (3% XE-60, 100 °C).

The crude product from the experiment described above was combined with the product resulting from a similar run (total 28.14 g) and distilled through a short Vigreux column to afford 19.5 g (50% yield from ester **27**) of ester **30** as a colorless oil, bp 75–77 °C (0.1 mm), which was >98% pure by VPC (5% SE-30, 120 °C): n^{20}_D 1.4694; IR λ_{max} (film) 3.42, 5.75 (C=O), and 8.64 μ; NMR 1.65 (s, 3 H, vinyl CH_3), 1.77 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.18 (m, $W_{h/2}$ = 7 Hz, 4 H, C-2 and C-7 CH_2's), 2.38 (m, $W_{h/2}$ = 3 Hz, 4 H, C-3 and C-6 CH_2's), 3.66 (s, 3 H, CO_2CH_3), and 5.22 ppm (t, J = 6 Hz, 1 H, C-5 vinyl proton).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.92; H, 9.26.

4-Methyl-*trans*-4-decen-8-ynal (31). A solution of 4.84 g (25 mmol) of the distilled ester **30** in 15 mL of dry THF was cooled to −70 °C with stirring in a flask equipped with a mechanical stirrer and a dry ice–acetone-cooled addition funnel; then a mixture of 10.5 mL (75 mmol) of a 3.54 M solution of Red-Al in benzene and 11 mL of dry THF was added from the cooled addition funnel over a period of 1 h. After stirring for 5 h under nitrogen at −70 °C, 3.45 mL (2.65 g, 60 mmol) of acetaldehyde was slowly added via syringe, and stirring was continued for an additional 10 min. The mixture was poured into 400 mL of 1.2 N hydrochloric acid and extracted with ether[24] to give 4.05 g (98% yield) of colorless oil consisting of 87% of the desired aldehyde **31** and 13% of the corresponding alcohol as shown by VPC (3% XE-60, 100 °C).

An analytical sample of **31** was obtained by preparative TLC (R_f 0.64, 2:1 pentane–ethyl acetate) followed by evaporative distillation at 70 °C (0.025 mm): n^{20}_D 1.4824; IR λ_{max} (film) 3.43, 3.69, and 5.76 (CHO) and 6.95 μ; NMR 1.58 (s, 3 H, vinyl CH_3), 1.71 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.10 (m, $W_{h/2}$ = 8 Hz, 4 H, C-2 and C-7 CH_2's), 2.38 (m, $W_{h/2}$ = 5 Hz, 4 H, C-3 and C-6 CH_2's), 5.21 (t, J = 6 Hz, 1 H, C-5 vinyl proton), and 9.80 ppm (s, 1 H, CHO).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.69; H, 9.75.

2-(4-Bromobutyl)-5-methylfuran (32). The method employed was an adaptation (developed by W. R. Bartlett) of a published procedure for alkylating 2-methylfuran.[19] A solution of 61.5 g (0.75 mol) of 2-methylfuran (distilled from calcium hydride, bp 64 °C) in 700 mL of dry THF was cooled to −30 °C and 350 mL (0.80 mol) of a 2.28 M solution of *n*-butyllithium in hexane was added via syringe. The mixture was stirred for 4 h at −20 to −30 °C under nitrogen; then the mixture was cooled to −60 °C and 467 g (2.16 mol) of cold (−25 °C) 1,4-dibromobutane, bp 82.0–83.5 °C (15 mm), was added in one portion. The resulting clear yellow solution was allowed to warm slowly to room temperature overnight; then it was poured into 250 mL of water overlaid with 300 mL of ether. The organic layer was washed with dilute hydrochloric acid and the aqueous layer was extracted with ether. After a base wash[24] the combined organic layers gave ca. 350 mL of orange liquid. A mixture of the crude product and 50 mg of hydroquinone was distilled through an 8-in. Vigreux column to give three fractions as follows: (a) 307 g of 1,4-dibromobutane, bp 36 °C (0.015 mm); (b) 30.3 g of a mixture of 1,4-dibromobutane and bromofuran **32**, bp 42–50 °C (0.015 mm); and (c) 95.2 g of bromofuran

32, bp 50 °C (0.015 mm). Fraction b was redistilled to afford a further 22.8 g of **32** bringing the total yield to 118 g (73%).

An analytical sample of the bromofuran **32,** bp 74–76 °C (0.3 mm), prepared as described above, was homogeneous by TLC and VPC (5% SE-30, 160 °C), and exhibited the following properties: n^{22}_D 1.5002; IR λ_{max} (film) 6.2, 6.4 (C=C of furan), 8.0, 8.2, 9.8 (furan), and 12.8 μ (furan); NMR 1.6–2.0 (m, 4 H, C-2 and C-3 CH_2's of side chain), 2.12 (s, 3 H, C-5 CH_3), 2.58 (t, J = 6 Hz, 2 H, C-1 CH_2 of side chain), 3.37 (t, J = 6 Hz, 2 H, C-4 CH_2 of side chain), and 5.82 ppm (s, 2 H, C-3 and C-4 protons of furan ring); TLC R_f 0.33 (benzene). The mass spectrum exhibited a parent peak at m/e 217 (M^+).

Anal. Calcd for $C_9H_{13}OBr$: C, 49.76; H, 6.04; Br, 36.83. Found: C, 49.82; H, 6.10; Br, 36.86.

1-Bromo-5,8-bis(ethylenedioxy)nonane (33). This procedure was developed by W. R. Bartlett. A mixture of 180 mL (200 g, 3.2 mol) of ethylene glycol, 3.0 g of *p*-toluenesulfonic acid monohydrate, ca. 100 mg of hydroquinone, and 500 mL of benzene was heated at reflux, to remove any water, in a flask equipped with a mechanical stirrer and a Dean-Stark trap fitted with a condenser. The flask was shielded from light and 111 g (0.51 mol) of the distilled bromofuran **32** was added. The mixture was heated at reflux under nitrogen for 43 h. Workup of the benzene layer using a base wash[24] afforded 158 g of pale yellow-brown liquid. A 69-g portion of this material was chromatographed on 1 kg of Florisil (100–200 mesh). Elution with hexane gave 9.5 g (19.7%) of unreacted bromofuran **32,** and elution with 15% ether in hexane gave 51 g (71% yield, 88% based on recovered furan **32**) of the bisketal **33** as a pale yellow oil which was >99% pure by VPC (3% XE-60, 160 °C): n^{24}_D 1.4853; IR λ_{max} (film) 7.6–8.3, 8.7–9.7, 10.5, 11.0, and 11.6 μ; TLC R_f 0.5 (3:2 ether–pentane). The mass spectrum exhibited a parent peak at m/e 323 (M^+).

An analytical sample of **33** was prepared by evaporative distillation at 140 °C (0.05 mm): NMR 1.22 (s, 3 H, C-9 CH_3). 1.56 (s, 4 H, C-6 and C-7 CH_2's), 1.5–2.1 (m, 6 H, C-2, C-3 and C-4 CH_2's), 3.35 (t, J = 6 Hz, 2 H, CH_2Br), 3.83 (s, 4 H, ketal CH_2's), and 3.85 ppm (s, 4 H, ketal CH_2's).

Anal. Calcd for $C_{13}H_{23}O_4Br$: C, 48.28; H, 7.17; Br, 24.74. Found: C, 48.39; H, 7.22; Br, 24.84.

5,8-Bis(ethylenedioxy)-1-iodononane (34). An adaptation of a published procedure[29] was employed. A mixture of 39.6 g (0.123 mol) of the chromatographed bisketal **33**, 26.4 g (0.176 mol) of dry sodium iodide, and 150 mL of dry 2-butanone was stirred under nitrogen for 40 min at 80 °C. The resulting mixture was poured into dilute aqueous sodium bicarbonate solution and extracted with ether using a wash with aqueous sodium thiosulfate solution followed by a base wash[24] to give 44.9 g (99% yield) of the bisketal iodide **34** as a nearly colorless liquid which was >99% pure by VPC (3% XE-60). An analytical sample was prepared by evaporative distillation at 145 °C (0.05 mm): NMR 1.30 (s, 3 H, C-9 CH_3), 1.45–2.0 (m, 6 H, C-2, C-3, and C-4 CH_2's), 1.70 (s, 4 H, C-6 and C-7 CH_2's), 3.20 (t, J = 6 Hz, 2 H, $-CH_2I$), and 3.94 ppm (s, 8 H, ketal CH_2's).

Anal. Calcd for $C_{13}H_{23}O_4I$: C, 42.18; H, 6.26; I, 34.28. Found: C, 42.40; H, 6.13; I, 34.54.

5,8-Bis(ethylenedioxy)nonyltriphenylphosphonium Iodide (35). A modification of a published procedure[30] was employed. A mixture of 1.13 g (3.05 mmol) of the bisketal iodide **34**, 1.14 g (4.35 mmol) of triphenylphosphine, and 5 mL of dry benzene was stirred under nitrogen for 11 h at 80 °C; then 20 mL of dry ether was added. The supernatant was decanted and the residual thick white oil was washed with 10 mL of dry ether. The oil was dissolved in 6 mL of dry acetone, cooled to 0 °C, and stirred while 30 mL of dry ether was slowly added. The supernatant was decanted and the residual colorless, crystalline salt was washed with 10 mL of dry ether. Drying at reduced pressure afforded 1.81 g (94% yield) of the phosphonium salt **35** as colorless microcrystals: mp 135–140 °C; IR λ_{max} ($CHCl_3$) 6.33, 6.78, 6.99, 9.02, and 14.07 μ; NMR 1.27 (s, 3 H, C-9 CH_3), 1.63 (s, 4 H, C-6 and C-7 CH_2's), 1.6–2.0 (m, 6 H, C-2, C-3, and C-4 CH_2's), 2.92 (m, $W_{h/2}$ = 24 Hz, 2 H, C-1 CH_2), 3.88 (s, 4 H, ketal CH_2's), 3.90 (s, 4 H, ketal CH_2's), and 7.7–8.1 ppm (m, 15 H, aromatic protons).

Anal. Calcd for $C_{31}H_{38}O_4PI$: C, 58.86; H, 6.06; P, 4.90; I, 20.06. Found: C, 59.00; H, 6.02 P, 4.79; I, 19.52.

This procedure has been performed on a much larger scale by P. A. Bartlett. Thus from 266 g of the bisketal iodide there was obtained 435 g (94% yield) of the phosphonium salt, mp 125–135 °C.

15,18-Bis(ethylenedioxy)-7-methyl-*trans,trans*-6,10-nonadecadien-2-yne (37). An adaptation of a published procedure[20] was employed. A dispersion of 4.45 g (7 mmol) of the phosphonium salt **35**, mp 135–140 °C, in 25 mL of dry THF was stirred under nitrogen while 7 mL (7.14 mmol) of a 1.02 M solution of phenyllithium in ether was slowly added. The resulting deep-red solution of ylide was cooled to −70 °C and a solution of 1.15 g (7 mmol) of aldehyde **31,** chromatographed on Florisil, >98% pure by VPC, in 10 mL of dry ether was added slowly via syringe. After stirring for 5 min at −70 °C, the solution was warmed to −30 °C and an additional 8 mL of phenyllithium solution was added. The mixture was stirred at −30 °C for 5 min and 1 mL of methanol was slowly added via syringe. A precipitate of triphenylphosphine oxide immediately formed. The mixture was stirred at room temperature for 2 h, then poured into water and extracted with ether,[24] and the crude product was triturated twice with pentane to afford 2.86 g of yellow oil consisting of about 65% of the desired product **37** as shown by NMR relative to triphenyl phosphite absorptions, and VPC (3% XE-60, 220 °C). Chromatography on Florisil (9:1 pentane–ether) gave 1.64 g (60% yield) of bisketal **37** as a colorless oil which was >95% pure by VPC (3% XE-60, 220 °C). An analytical sample was obtained by preparative TLC (R_f 0.32, 2:1 pentane–ethyl acetate) followed by evaporative distillation at 190 °C (0.01 mm): IR λ_{max} (film) 3.45, 6.90, 7.30, 9.58, 10.30, and 10.52 μ; NMR 1.39 (s, 3 H, C-19 CH_3), 1.63 (s, 3 H, vinyl CH_3), 1.65 (br m, 10 H, C-4, C-13, C-14, C-16, and C-17 CH_2's), 1.75 (t, J = 2.5 Hz, 3 H, C-1 CH_3), 2.03 (m, $W_{h/2}$ = 11 Hz, 8 H, C-5, C-8, C-9, and C-12 CH_2's), 3.94 (s, 8 H, ketal CH_2's), 5.19 (t, J = 6 Hz, 1 H, C-6 vinyl proton), and 5.41 ppm (m, $W_{h/2}$ = 9 Hz, 2 H, C-10 and C-11 vinyl protons).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 74.10; H, 9.70.

13-Methyl-*trans,trans*-9,13-nonadecadien-17-yne-2,5-dione (38). A mixture of 2.75 g of crude bisketal **37**, 65% pure by NMR, 100 mL of methanol, and 30 mL of 0.1 N hydrochloric acid was stirred at 40 °C for 6 h under nitrogen. The mixture was cooled to room temperature and basified with solid sodium bicarbonate. The solvent was removed at reduced pressure and the residue was diluted with water. Extraction with ether[24] afforded 2.25 g of crude dione **38** as a pale yellow oil.

A sample of comparable material from another run was purified by preparative TLC (R_f 0.25, 2:1 pentane–ethyl acetate) followed by evaporative distillation at 190 °C (0.01 mm) to afford an analytical specimen as a colorless oil which was >98% pure by VPC (3% XE-60, 200 °C): IR λ_{max} (film) 3.43, 5.82 (C=O), 7.32, and 10.30 μ; NMR 1.62 (s, 3 H, vinyl CH_3), 1.78 (t, J = 2.5 Hz, 3 H, C-19 CH_3), 1.78 (m, $W_{h/2}$ = 12 Hz, 4 H, C-7 and C-16 CH_2's), 2.10 (m, $W_{h/2}$ = 8 Hz, 8 H, C-8, C-11, C-12, and C-15 CH_2's), 2.21 (s, 3 H, C-1 CH_3), 2.46 (t, J = 7 Hz, 2 H, C-6 CH_2), 2.70 (s, 4 H, C-3 and C-4 CH_2's), 5.21 (t, J = 6 Hz, 1 H, C-14 vinyl proton), and 5.43 ppm (m, $W_{h/2}$ = 10 Hz, 2 H, C-9 and C-10 vinyl protons).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.40; H, 9.88.

3-Methyl-2-(7-methyl-*trans,trans*-3,7-tridecadien-11-ynyl)-2-cyclopentenone (39). A solution of 2.25 g of the aforementioned crude dione **38** in 30 mL of methanol was added to 70 mL of 2% aqueous sodium hydroxide, and the resulting mixture was heated at reflux for 18 h under nitrogen. The methanol was removed at reduced pressure; then the residue was diluted with water and extracted with ether[24] to give 2.20 g of yellow oil. Chromatography on Florisil (9:1 pentane–ether) afforded 0.92 g (46% yield based on aldehyde **31**) of cyclopentenone **39** as a colorless oil which was >95% pure by VPC (3% XE-60, 210 °C). Analytical VPC (3% XE-60, 160 °C) showed two components with retention times of 35.0 and 36.5 min in a ratio of 97:3 corresponding to the trans product **39** and the cis-3 isomer as determined by coinjection with a sample enriched in cis isomer obtained from a normal Wittig reaction of **31** with **36.**

An analytical specimen was obtained from a sample of comparable material from another run by preparative TLC (R_f 0.40, 4:1 pentane–ethyl acetate) followed by evaporative distillation at 190 °C (0.05 mm): IR λ_{max} (film) 3.43, 5.86 (α,β-unsaturated C=O), 6.05 (C=C), 6.94, 7.20, and 10.29 μ (trans RCH=CHR); UV λ_{max} (MeOH) 235 nm (ϵ 10 400); NMR 1.61 (s, 3 H, side-chain vinyl CH_3), 1.78 (t, J = 2.5 Hz, 3 H, C-13 CH_3), 1.80 (m, $W_{h/2}$ = 8 Hz, 2 H, C-10 CH_2), 2.05 (s, 3 H, enone vinyl CH_3), 2.12 (m, $W_{h/2}$ = 8 Hz, 10 H, side-chain C-1, C-2, C-5, C-6, and C-9 CH_2's), 2.43 (m, $W_{h/2}$ = 6 Hz, 4 H, cyclopentenone CH_2's), 5.21 (t, J = 6 Hz, 1 H, C-8 vinyl proton), and 5.42 ppm (m, $W_{h/2}$ = 9 Hz, 2 H, side-chain C-3 and C-4 vinyl protons). The mass spectrum (70 eV) exhibited peaks at m/e 284 (M^+), 269 (M − 15), and 163 (parent, M − 121).

Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.33; H, 9.77.

1,3-Dimethyl-2-(7-methyl-*trans,trans*-3,7-tridecadien-11-ynyl)-2-cyclopentenol (6). A few crystals of 1,10-phenanthroline were added to a solution of 210 mg (0.74 mmol) of enone **39** (>95% pure by VPC) in 5 mL of dry ether; then ca. 0.5 mL of a 2.0 M solution of methyllithium in ether was slowly added via syringe until a yellow brown color persisted. The mixture was stirred for 2 min at room temperature under nitrogen, and then excess methyllithium was destroyed by careful addition of water. The resulting mixture was diluted with water and extracted with ether[24] to afford 219 mg (99% yield) of crude cyclopentenol **6** as a pale yellow oil: IR λ_{max} (film) 2.70–3.22 (OH), 3.38, 6.92 (C=C), 7.20, 9.20, and 10.30 μ (trans RCH=CHR); NMR 1.37 (s, 3 H, C-1 CH_3), 1.65 (s, 3 H, side-chain vinyl CH_3), 1.72 (t, J = 2.5 Hz, 3 H, C-13 CH_3), 1.80 (m, $W_{h/2}$ = 10 Hz, 4 H, C-5 CH_2 of cyclopentenol and C-10 CH_2), 1.88 (s, 3 H, ring vinyl CH_3), 2.20 (m, $W_{h/2}$ = 9 Hz, 12 H, allylic CH_2's), 5.23 (t, J = 6 Hz, 1 H, C-8 vinyl proton), and 5.46 ppm (m, $W_{h/2}$ = 9 Hz, 2 H, side-chain C-3 and C-4 vinyl protons).

VPC examination (3% XE-60, 170 °C) of this material showed two peaks in a ratio of 3:1 which accounted for 95% of the total peak area and which presumably represent the two possible dehydration products. Since the enol **6** is highly susceptible to dehydration, a combustion analysis was not obtained and the crude material was used directly in the cyclization studies.

Cyclization of Trienynol 6 with Trifluoroacetic Acid and Ethylene Carbonate in 1,2-Dichloroethane. 3-Methyl-*A*-nor-3-pregnen-20-one (40). A mixture of 219 mg (0.70 mmol) of the trienynol **6**, 95% pure by VPC, 22.0 g of 1,2-dichloroethane (distilled from phosphorus pentoxide), and 2.20 g of ethylene carbonate (crystallized from the melt) was stirred under nitrogen at 0 °C while 0.80 mL (1.23 g, 10.8 mmol) of trifluoroacetic acid (bp 71–73 °C) was added over a 2-min period. The resulting mixture, which eventually turned deep red, was stirred at 0 °C for 1.5 h; then an additional 0.80 mL of trifluoroacetic acid was added and stirring was continued for 1.5 h at 0 °C. The mixture was diluted with 20 mL of a 10% solution of potassium carbonate in 1:1 methanol–water and stirred for 1 h at room temperature. The mixture was poured into water and extracted with ether[24] to give 238 mg of dark orange oil which consisted of 70% of the 17β ketone **40**, 13% of the 17α isomer, 6% corresponding to the dehydration product of unreacted trienynol **6**, 5% of an unidentified conponent,[21] and 6% of minor components[21] as shown by VPC (3% XE-60, 170 °C). Chromatography on 12 g of Florisil (9:1 pentane–ether) afforded 158 mg (71% yield based on cyclopentenone **39**) of a 5:1 mixture of the 17β **40** and 17α ketones as a colorless oil which was 95% pure by VPC. A sample of this material was recrystallized from pentane at −20 °C to give ketone **40** as colorless leaflets, mp 82–88 °C, which contained 9.5% of the 17α isomer by VPC. A further recrystallization from pentane gave colorless crystals, mp 88–89 °C, containing <5% of the 17α isomer: IR λ_{max} ($CHCl_3$) 3.42, 5.86 (C=O), 6.90, and 7.40 μ; NMR 0.65 (s, 3 H, C-19 CH_3), 0.92 (s, 3 H, C-18 CH_3), 1.58 (s, 3 H, vinyl CH_3), 2.13 (s, 3 H, C-21 CH_3), and 0.7–2.6 ppm (methylene envelope, 20 H). The mass spectrum (70 eV) exhibited major peaks at m/e 300 (M^+), 285 (parent, M − 15), and 257 (M − 43).

A sample of the chromatographed ketones (5:1 17β/17α) was evaporatively distilled at 190 °C (0.05 mm) to give an analytical sample which exhibited one spot on TLC (R_f 0.69, 2:1 pentane–ethyl acetate).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.77; H, 10.62.

***dl*-Progesterone (8).** A solution of 150 mg (0.5 mmol) of the chromatographed tetracyclic ketones **40** in 15 mL of methanol and 5 mL of methylene chloride was stirred at −70 °C in a Rubin ozonizer[31] while 14 mL of methylene chloride saturated with ozone (0.55 mmol) at −70 °C was slowly added under nitrogen pressure. The resulting mixture was stirred for 2 min at −70 °C and warmed to −15 °C; then 10 mL of acetic acid, 2 mL of water, and 1 g of zinc dust were added. The mixture was stirred for 30 min at room temperature, filtered, and diluted with water. Extraction with ether using a base wash[24] afforded 146 mg (88% yield) of triketone **41** as a nearly colorless oil which exhibited one major spot on TLC (R_f 0.26, 2:1 pentane–ethyl acetate): IR λ_{max} (film) 3.42 and 5.88 μ (C=O).

The crude triketone was dissolved in 5 mL of methanol and stirred under nitrogen while 2 mL of a 5% solution of potassium hydroxide in methanol was added via syringe. The resulting mixture was stirred at room temperature for 20 h, poured into water, and extracted with ether[24] to give 126 mg of pale yellow oil, VPC examination (3% XE-60, 240 °C) of which showed 80% of a 9:1 mixture of 17β-/17α-progesterone, 2% of **androst-4-ene-3,17-dione (9)**, 5% of an unidentified component, and 13% of minor impurities. Preparative TLC (3:2 pentane–ethyl acetate) afforded 71 mg (45% yield) of an 85:15 mixture of 17β-/17α-progesterone (**8**) as a crystalline solid which was >95% pure by VPC. Recrystallization from methanol–ether produced colorless plates, mp 180–183 °C, which contained <5% of 17α-progesterone by VPC. A further recrystallization from methanol resulted in colorless prisms, mp 182–185 °C. On admixture with an authentic specimen of *dl*-progesterone,[22] mp 182–185 °C, the mp was 182.0–185.5 °C. The specimen derived from **41** had the following spectral properties: IR λ_{max} (CH_2Cl_2) 3.40, 5.88 (C=O), 6.00 (α,β-unsaturated C=O), 7.40, 10.50, and 11.53 μ; NMR 0.67 (s, 3 H, C-19 CH_3), 1.18 (s, 3 H, C-18 CH_3), 2.12 (s, 3 H, C-21 CH_3), 0.7–2.6 (methylene envelope), and 5.74 ppm (s, 1 H, C-4 vinyl proton). The mass spectrum[32] (70 eV) exhibited major peaks at m/e 314 (M^+), 299 (M − CH_3), 272 (M − OC_2H_5 from ring A), 229 (M − ring D with H transfer), and 124 (parent peak, ring B cleavage with 2 H transfer).

The IR (CH_2Cl_2), NMR, and mass spectra of the synthetic sample were identical with the corresponding spectra of naturally derived progesterone.

Cyclization of Trienynol 6 with Trifluoroacetic Acid in Pentane. 3-Methyl-20-(trifluoroacetoxy)-*A*-nor-3,17-pregnadiene (42). A solution of 175 mg (0.55 mmol) of trienynol **6**, 95% pure by VPC, in 175 mL of dry 7.5:1 pentane–1,2-dichloroethane was stirred at 0 °C under nitrogen while 1.0 mL (1.54 g, 13.5 mmol) of trifluoroacetic acid was added over a period of 2 min via syringe. The resulting dark orange-brown mixture was stirred for 1 h at 0 °C and poured into water. Pentane extraction using a base wash[24] afforded 230 mg of dark orange oil which exhibited two major peaks of retention times 2.6 (20%) and 5.0 min (76%) on VPC (3% XE-60, 180 °C), and essentially a single spot on TLC (R_f 0.69, 4:1 pentane–ethyl acetate). The crude product was purified by preparative TLC (2:1 pentane–ethyl acetate) to give 171 mg (78% yield) of the trifluoroacetate **42** as a pale yellow oil which exhibited the same two major peaks on VPC, and <1% of C-12 ketones **40**. Analytical TLC exhibited a single spot suggesting that the 2.6-min VPC retention time peak is a thermal decomposition product. Evaporative distillation at 150 °C (0.01 mm) afforded 150 mg of **42** as a clear, colorless oil, VPC examination of which showed no change in composition: IR λ_{max} (film) 3.43, 5.62 (C=O), 7.40, 8.21, 8.60, 8.80, 12.96, and 13.52 μ; NMR 0.89 (s, 3 H, C-18 CH_3), 0.92 (s, 3 H, C-19 CH_3), 1.56 (s, 3 H, vinyl CH_3), 1.96 (s, 3 H, C-21 vinyl CH_3), and 0.8–2.6 ppm (methylene envelope).

Anal. Calcd for $C_{23}H_{31}O_2F_3$: C, 69.71; H, 7.83. Found: C, 72.19; H, 8.35.

The poor agreement of the combustion analysis suggests partial elimination of the trifluoroacetate group upon redistillation.

***dl*-Δ⁴-Androstene-3,17-dione (9).** A solution of 265 mg (0.67 mmol) of crude enol trifluoroacetate **42**, prepared as described above, in 20 mL of 1:1 methanol–methylene chloride was cooled to −70 °C under nitrogen in a Rubin ozonizer[31] and 60 mL of a saturated solution of ozone in methylene chloride at −70 °C (about 1.35 mmol of ozone) was added under nitrogen pressure. After stirring the mixture at −70 °C for 15 min and at −15 °C for 15 min, 5 mL of acetic acid, 1 mL of water, and 2 g of zinc dust were added, and stirring was continued for 1 h at room temperature. The resulting mixture was diluted with water, filtered, and extracted with ether[24] to give 172 mg (84% yield) of crude triketones **43** as a colorless oil which exhibited three peaks of retention times 2.4, 4.0, and 4.8 min in a ratio of 3:2:5 on VPC (6-ft 3% XE-60, 240 °C): IR λ_{max} (film) 5.75 and 5.85 μ (C=O).

The crude triketones **43** were not characterized further, but were cyclized directly by dissolution in 20 mL of methanol, addition of 25 mL of a 5% solution of potassium hydroxide in methanol, and stirring the mixture for 20 h at room temperature under nitrogen. The resulting mixture was neutralized with acetic acid and the solvent was removed at the rotary evaporator. The residual liquid was diluted with water and extracted with ether[24] to afford 120 mg (74% yield) of pale yellow oil consisting of 78% of androstenedione **9**, identified by coinjection with authentic ***dl*-Δ-androstene-3,17-dione (9)**,[23] 15% of an unidentified component, and 7% of ***dl*-progesterone (8)** with retention times of 4.3, 5.0, and 6.0 min, respectively, as shown by VPC (6-ft 3% XE-60, 240 °C). Preparative TLC (extended elution, 1:1 pentane–ethyl acetate, R_f 0.50–0.60) yielded 100 mg of dione **9** as a colorless, crystalline solid which was 90% pure by VPC. Crystallization from

1:1 pentane–ether at −20 °C gave microcrystals, mp 126–129 and 135–138 °C.[33] Recrystallization from isopropyl ether–pentane gave colorless crystals: mp 128–130 °C; IR λ_{max} ($CHCl_3$) 3.40, 5.75 (C=O), 5.95 (α,β-unsaturated C=O), and 6.17 μ; NMR 0.83 (s, 3 H, C-18 CH_3), 1.20 (s, 3 H, C-19 CH_3), 1.0–2.5 (methylene envelope), and 5.76 ppm (br s, 1 H, C-4 vinyl proton); mass spectrum (70 eV) *m/e* 286 (M^+), and 244 (M − 42, from ring A).

The IR spectrum of **9** was identical with that of an authentic specimen[23] and a mixture melting point was undepressed (128.0–130.5 °C).

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Molecular Structures of Substrates and Inhibitors of Δ^5-3-Keto Steroid Isomerase and Their Relevance to the Enzymatic Mechanism

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Abstract: The crystal structures of a substrate, an acetylenic suicide substrate, and an allenic inhibitor of the enzyme Δ^5-3-keto steroid isomerase of *Pseudomonas testosteroni* (EC 5.3.3.1) have been determined. The enzyme catalyzes intramolecular proton transfer from C(4) to C(6), converting Δ^5- to Δ^4-3-keto steroids. The overall conformations of the acetylenic and allenic seco steroids are very much like those of substrate and product. Detailed three-dimensional parameters are given. These studies, together with the known structure of the Δ^4-3-keto steroid product have led to some suggestions on the mechanisms of this enzyme. It is proposed that binding of the C-3 carbonyl group of substrate to the enzyme ensures the correct conformation of the A and B rings for 4β hydrogen abstraction, leading to a $\Delta^{3,5}$-dienol. The conformations of the A and B rings will then dictate whether or not a proton is added at C(6) rather than at C(4). The acetylenic seco steroid is thought to bind in a similar manner and is converted enzymatically to the allenic seco steroid, which then alkylates and so inactivates the enzyme.

The Δ^5-3-keto steroid isomerase of *Pseudomonas testosteroni* (EC 5.3.3.1)[2a,b] catalyzes the conversion of Δ^5-3-keto steroids to Δ^4-3-keto steroids via β-face intramolecular proton transfer from C(4) to C(6) (Scheme I). Both the catalytic mechanism and the specificity of this enzyme have been studied in some detail.[3] The rate-limiting step in the reaction has been

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